Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 25224 WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP2003/008229	International filing date (*day/month/year*) 25 July 2003 (25.07.2003)	Priority date (*day/month/year*) 26 July 2002 (26.07.2002)
International Patent Classification (IPC) or national classification and IPC A61K 38/18		
Applicant EPOPLUS GMBH & CO. KG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26 February 2004 (26.02.2004)	17 November 2004 (17.11.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP2003/008229

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-27, 29-59, as originally filed

pages _____, filed with the demand

pages 28, filed with the letter of 18 October 2004 (18.10.2004)

☒ the claims:

pages _____, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages 1-43, filed with the letter of 18 October 2004 (18.10.2004)

☒ the drawings:

pages 1/15-15/15, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 24-32, 38-43

because:

☒ the said international application, or the said claims Nos. 24-32, 38-43 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. _____ .

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes III.1 and IV

Box III

1. Claims 24 to 32 and 38 to 43 relate to subject matter which, in the opinion of this Authority, falls under PCT Rule 67.1(iv). Consequently no expert opinion has been established regarding the industrial applicability of the subject matter of these claims (PCT Article 34(4)(a)(i)).

Box IV

2. The Examining Authority has determined that this international application contains multiple inventions or groups of inventions which are not linked by a single general inventive concept (PCT Rule 13.1). These are as follows:

   1. Claims 1-14, 24-28, 29-32 (in part) and 33-43:

      Use of EPO in a dose of 500 to 2000 units per week per patient for the stimulation of endothelial precursor cells and for the treatment of diseases; also corresponding pharmaceutical compositions.

   2. Claims 15-23 and 29-32 (in part):

      Use of EPO for the production of transplantable endothelial cell preparations, for the production of cell-containing organ and tissue systems, and for the production of heart valves.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes III.1 and IV

The reasons for this are as follows:

Judging from the claims and the description, the problem addressed by the present invention is that of providing agents and methods for improved stimulation of endothelial precursor cells and for the treatment of related diseases, and of providing endothelial cell preparations. The proposed solution involves the administration of EPO in general, and also a dose of 500 to 2000 units of EPO per week per patient. Thus, *a priori*, there is no unity of invention. Irrespective of this, mitogenic and migratory effects of EPO on endothelial cells and its angiogenic effect are described in WO 98/10650 A, US-A-5 980 887, BUEMI M et al. (J. Nephrol.) and KRAUSE K et al. (European Heart Journal). Since the use of EPO for the stimulation of endothelial cells - including the formation of new blood vessels - is already known, there is no general inventive concept linking inventions 1 and 2. The application fails to meet the requirement of unity of invention (PCT Rule 13.1) because there is no technical relationship between the inventions involving one or more of the same or corresponding special technical features (PCT Rule 13.2).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-23, 29-32, 43	YES
	Claims	24-28, 33-42	NO
Inventive step (IS)	Claims	1-3	YES
	Claims	4-23, 29-32, 43	NO
Industrial applicability (IA)	Claims	1-23, 33-37	YES
	Claims		NO

2. Citations and explanations

3. Reference is made to the following international search report citations and to the passages indicated in the search report:

D1: WO 03/057242 A

D2: WO 02/14356 A

D3: US 2002/065214 A1

D4: WO 00/61164 A

D5: WO 98/10650 A

D6: US-A-5 980 887

D7: NEPHROLOGY DIALYSIS TRANSPLANTATION, Vol. 12(9), 1997, page A190

D8: JOURNAL OF NEPHROLOGY, 2002, ITALY, Vol. 15, No. 2, 2002, pages 97-103

D9: INTERNATIONAL JOURNAL OF HEMATOLOGY, Vol. 70, No. 1, pages 1-6

D10: EUROPEAN HEART JOURNAL, Vol. 22, No. Abstract Supplement, September 2001 (2001-09), page 154

D11: NEPHROLOGY DIALYSIS TRANSPLANTATION, Vol. 10(2), pages 74-79

D12: DATABASE BIOSIS [online]; 2002, KASHIWAGI M et al.: "Hypertension in a pregnancy with renal anemia after recombinant human erythropoietin (rhEPO) therapy"

D13: DATABASE BIOSIS [online]; 1997, CONRAD KIRK P et al.: "Placental cytokines and the pathogenesis of preeclampsia"

D14: WO 03/037273 A

D15: DATABASE EMBASE [online]; 2000, CASES A: "Recombinant human erythropoietin treatment in chronic renal failure: Effects on hemostasis and vasculature"

D16: DATABASE MEDLINE [online]; 1996, BRAGA J et al.: "Maternal and perinatal implications of the use of human recombinant erythropoietin"

D17: WO 02/085940 A

D18: DATABASE BIOSIS [online]; 2001, ARCASOY MURAT O et al.: "Erythropoietin (EPO) stimulates angiogenesis *in vivo* and promotes wound healing"

D19: WO 89/07944 A

D20: WO 92/15323 A

D21: US-A-4 992 419

D22: US-A-5 198 417

D23: DATABASE BIOSIS [online]; 1998, ALVAREZ ARROYO MARIA VICTORIA et al.: "Role of vascular endothelial growth factor on erythropoietin-related endothelial cell proliferation"

3.1 Document D1 discloses the use of EPO for the treatment of heart failure. Assuming that the priority claim is valid, D1 is not regarded as prior art for the purposes of the international preliminary examination.

3.2 Document D2 describes the use of EPO for the treatment of chronic heart failure, including in conjunction with kidney failure, with 5, 75, 150 and 200 IU (international units) per kilogram, once to three times a week (claims 35 and 36).

3.3 Document D3 discloses the use of EPO in conjunction with an iron compound to improve the functioning of the heart. The dose is 500 to 10000 IU per week.

3.4 Document D3 discloses pharmaceutical compositions containing EPO for the prevention of hypotonia, ischemia, heart attacks and inflammation.

3.5 Document D5 describes how certain doses of EPO protect endothelial cells from damage, and how it has been shown that EPO has a mitogenic and migratory effect on endothelial cells, which is a key step for angiogenesis. Types of damage that can be treated by the invention also include those caused by inflammation, heart diseases and atherosclerosis. EPO is used to treat anaemia (in conjunction with chronic kidney failure).

3.6 Document D6 describes a method for treating damaged blood vessels, in which EPO is administered as an endothelial cell mitogen, and endothelial precursor cells are isolated and re-administered. The method can also be used to treat various types of ischemia (e.g. renal).

3.7 Document D7 describes the protective effect of EPO against atherosclerosis in hypercholesterolemic rabbits.

3.8 Document D8 describes the role of rEPO in chronic inflammatory diseases (neopterin reduction) and the stimulation of endothelial cells (angiogenesis), apart from the usual treatment of anaemia (in patients with chronic kidney failure). There are indications that EPO is suitable for wound healing. The synergy of VEGF and EPO is also described.

3.9 Document D9 discloses the angiogenic activity of EPO

and the stimulation of the proliferation and migration of endothelial cells.

3.10 Document D10 discloses the angiogenesis potential of EPO.

3.11 Document D11 describes the connection between EPO treatment and high blood pressure.

3.12 Document D12 shows that EPO treatment increases blood pressure in pregnant women.

3.13 Document D13 discloses a hypothesis linking preeclampsia with placental cytokines.

3.14 Document D14 discloses the use of EPO for the treatment of acute ischemic kidney failure, involving subpolycythemic doses. The treatment results in cell repair (example 6). Assuming that the priority claim is valid, D14 is not regarded as prior art for the purposes of the international preliminary examination.

3.15 Documents D15 and D16 disclose the use of EPO for the treatment of chronic kidney failure.

3.16 Document D17 discloses EPO derivatives for the treatment of various diseases, including wound healing, kidney insufficiency, cardiovascular diseases and rejection reactions.

3.17 Document D18 shows that EPO has a pro-angiogenic effect and promotes wound healing.

3.18 Document D19 discloses neovascularisation implants which can be coated with cells that produce EPO.

3.19 Document D20 discloses a method for increasing the cell population by *ex vivo* stimulation with a morphogen. EPO is one of the relevant factors in the haemopoietic system.

3.20 Document D21 discloses pharmaceutical compositions containing EPO and L-arginine.

3.21 Document D22 discloses the co-administration of EPO and GM-CSF.

3.22 Document D23 discloses the synergistic interaction of EPO and VEGF.

4. Novelty

4.1 Claims 1 to 14 relate to the use of erythropoietin in the production of a pharmaceutical composition containing a dose of 500 to 2000 units of EPO per week per patient for the treatment of various diseases. Since none of the cited documents disclose the use of such doses for the treatment of the diseases mentioned, the subject matter of claims 1 to 14 and of dependent claims 29 to 32 and claim 43 appears to be novel.

4.2 Claims 15 to 23 relate to the use of EPO in the production of transplantable endothelial cell preparations, the production of cell-containing organ and tissue systems, and the production of heart valves. Since none of documents D2 to D23 disclose methods of this type, the subject matter of these claims appears to be novel.

4.3 Claims 24 and 38 relate to the use of erythropoietin in a dose of 500 to 2000 units per week per patient

for the stimulation of endothelial cells and of vasculogenesis. However, since this definition also covers heart diseases and ischemias (e.g. D5 and D6, original claims), the subject matter of these claims and of claims 25 to 28 and 38 to 42 does not appear to be novel over (at least) documents D2 and D3.

4.4 Claims 33 and 34 relate to a pharmaceutical composition containing erythropoietin in a dose of 500 to 2000 units of EPO per week per patient, either alone or in conjunction with other active substances. Claim 34 does not appear to be novel over D2 or D3. Since it is not clear whether the claims relate to one-off doses, the subject matter of claims 33 to 37 also appears to lack novelty over documents D21, D22 and D23.

5. Inventive step

5.1 Claims 1 and 2 relate to the use of erythropoietin in the production of a pharmaceutical composition containing a dose of 500 to 2000 units of EPO per week per patient for the treatment of chronic or acute kidney insufficiency. Document D2 can be regarded as the closest prior art because it discloses the use of EPO for the treatment of renal anaemias due to chronic kidney insufficiency.

The application shows that using the claimed subpolycythemic doses to treat chronic or acute kidney insufficiency results in kidney tissue regeneration. Since the prior art treatment involves compensating for a lack of EPO in the body and at the same time increasing the haematocrit values, the use of subpolycythemic doses does not seem obvious.

5.2 Claim 3 relates to the use of erythropoietin in the production of a pharmaceutical composition containing a dose of 500 to 2000 units of EPO per week per patient for wound healing. Document D18, which is regarded as the closest prior art, discloses the angiogenic function of EPO in wound healing, and differs in that a different dose is used.

The problem addressed is that of providing an improved wound treatment. Since just such an effect is shown to be achieved, the subject matter of claim 3 appears to be inventive.

5.3 Claim 4 relates to the use of erythropoietin in the production of a pharmaceutical composition containing a dose of 500 to 2000 units of EPO per week per patient for the treatment of various diseases.

On the basis of documents D5 to D7 and D11 to D13, which disclose the treatment of the diseases in question with EPO, the problem addressed is that of providing an improved treatment. Since there is no indication of any actual improvement, the subject matter of claims 4 to 14, 29 to 32 and 43 does not appear to be inventive.

5.4 The subject matter of claims 15 to 23 has no supporting data in the description and appears to be an arbitrary use of the properties of EPO which are known from documents D5, D6, D8, D9, D10, D19 and D20, and therefore does not appear to be inventive.